Rectal Adenocarcinoma: Proposal for a Model Based on Pretreatment Prognostic Factors

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Objective: Currently the choice of chemotherapy regimen in rectal cancer is made prior to surgery in contrast to colon cancer where it is made postoperatively after the pathological stage has been determined. If we could identify which are the important pretreatment prognostic factors in rectal cancer, we could then target those patients with unfavorable features to investigate potentially more effective preoperative chemotherapy regimens aimed at those with unfavorable features. The present study aimed to determine pre-treatment prognostic factors that are associated with an unfavorable outcome.

Methods: A retrospective review of 99 rectal cancer patients operated at the Auxilio Mutuo Hospital, San Juan, Puerto Rico, and the San Pablo Hospital, Bayamón, Puerto Rico was done. Socio-demographic, clinical and treatment data were collected.

Results: Of the 99 cases, 54% were males. The mean age ± standard deviation was 62.2 ± 10.4. In age-adjusted Cox model, male gender (HR [95%CI]: 3.32 [1.09-10.13]), mucinous carcinoma (HR [95%CI]: 3.67 [1.25-10.77]), and clinical stages II & III (HR [95%CI]: 8.19 [1.08-62.08]) were predictors of poor prognosis. In the multivariate age-adjusted analysis, a tendency towards a poorer prognosis was observed for male patients (HR: 2.60), carcinoembryonic antigen level ≥ 5ng/ml (HR: 2.55), mucinous carcinoma (HR: 2.96), and clinical stages II & III (HR: 4.96), although results were not statistically significant (p>0.05).

Conclusion: Although current therapeutic results are relatively favorable with preoperative 5-fluorouracil and radiotherapy, future clinical trials should address the management of those cases with adverse pretreatment prognostic factors so that they can be treated with potentially more effective albeit more toxic chemotherapy regimens. [*P R Health Sci J 2012;2:52-58*]

Key words: Rectal cancer, Hispanic, Prognostic Factors, Clinicopathologic, Survival

Patients with rectal carcinoma tend to have a high local relapse rate when managed with conventional surgery (1-2). Although the introduction of the total mesorectal excision (TME) surgical technique has significantly reduced the high local relapse rate in rectal cancer, preoperative radiation with or without added chemotherapy ("neoadjuvant chemoradiation") reduces the risk even further and is the current standard of care for rectal carcinomas in many centers (3-8). The most commonly used preoperative chemotherapy regimen is 5-fluorouracil (5-FU) continuous infusion, which in combination with radiotherapy has significantly reduced the local relapse rate (9-11). Yet, there are newer drugs and combinations such as FOLFOX and FOLFIRI that are significantly more effective in the metastatic colorectal cancer setting (12-13). Because of concerns in regards to these drugs' toxicity, these regimens are being investigated but are not yet considered as the standard of care for neoadjuvant rectal cancer therapy (14-15).

Identifying which are the most important prognostic factors in rectal cancer would allow selection of patients with unfavorable features for whom the newer chemotherapy regimens may be of greater benefit, at the same time sparing those with favorable prognostic features from the toxicity of the newer combinations. Numerous studies have assessed the prognostic factors in colorectal carcinoma but few have focused exclusively on rectal cancer (16-58). Therefore, it is not clear whether the prognostic factors of colon and rectal cancer are equivalent. There are some data which suggest that adenocarcinoma of the rectum is biologically different from that arising in colon (59). Furthermore, the small number of studies that have examined the prognostic factors in rectal cancer separately from colon cancer have emphasized those

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features observed after neoadjuvant chemoradiation therapy has been completed rather than prior to such therapy (10, 34, 37, 49). However, information regarding the relevant preoperative prognostic features is needed when faced with the decision as to what type of neoadjuvant chemotherapy regimen might be preferable. Thus, the aim of this study was to assess the association between pretreatment prognostic factors and unfavorable outcomes in rectal cancer.

Methods

A retrospective review of 123 patients with rectal cancer operated at the Auxilio Mutuo Hospital, San Juan, Puerto Rico, and San Pablo Hospital, Bayamón, Puerto Rico from January 2000 through January 2007 was performed. The study population included all patients operated by two of the authors (IAE, GQ), both experienced colorectal surgeons. Of the 123 cases, 7 presented either with stage IV disease or with unresectable T4 tumors and were excluded from this analysis. Seventeen cases had missing data for carcinoembryonic antigen (CEA) levels. Thus, the study group consisted of 99 rectal adenocarcinoma cases with stage I-III presentations. The study was approved by the Institutional Review Board of Auxilio Mutuo Hospital.

The following data were collected and analyzed as potential pretreatment prognostic factors: gender, age (as a continuous variable), histologic grade (well-, moderately-, or poorly differentiated), mucinous histology (yes or no), clinical stage (I, II, or III), preoperative carcinoembryonic antigen (CEA) level (<5 or ≥5 ng/ml), and lymphovascular invasion (yes or no). The level of the primary tumor within the rectum was calculated mostly by rigid proctoscopy and/or digital rectal examination and expressed as the distance from the anal verge. Low rectum was defined as 0-5 cm from the anal verge, mid-rectum as 6-10 cm and high rectum as 11-15 cm. The type of surgery performed (abdomenoperineal resection [APR], low anterior resection [LAR], local or transanal excision or others [pelvic exenteration, subtotal colectomy]) was also evaluated.

Computed tomography (CT) scans of abdomen and pelvis as well as chest x-rays or CT of chest was performed to determine preoperative clinical staging in all cases. Preoperative endorectal ultrasound (EUS) and digital rectal exam were performed for local staging in 47 cases of rectal cancer. Preoperative EUS was not done on 52 cases due to the following reasons: 27 cases had tumors in the upper part of the rectum, 2 had occlusion of rectal lumen, 2 had a preoperative diagnosis of benign polyps, and 21 for various other reasons. Preoperative local staging was performed with digital rectal exam and CT scans in the 52 patients who did not have a preoperative EUS. Evaluation for systemic disease was carried out with CT scans.

A low anterior resection was performed in patients in whom it was possible to save the sphincter; otherwise, an abdominoperineal resection was done. The surgical technique used was total mesorectal excision (TME) except in those cases that had a local excision. Highly selected cases with low rectal lesions were managed with full thickness local transanal excision.

Finally, chemoradiation was utilized preoperatively essentially for all T3 lesions with low and mid-rectal presentations. The type of chemotherapy used consisted primarily of 5-FU in varying schedules. All patients who started chemoradiation were able to proceed to surgery.

Statistical analysis

Descriptive statistics were used to portray the study group using the mean (standard deviation, SD) or median (25th and 75th percentiles) for continuous data; frequencies and proportions were used for categorical data. A comparison of selected pretreatment prognostic factors between rectal and colon cases was performed using Student's t test (or Mann-Whitney-Wilcoxon test if appropriate) and the Pearson chi-square statistic (or Fisher's exact test if applicable).

Failure free survival was defined as the length of time from surgery to first evidence of relapse or lethal toxicity from treatment. Data were censored at the last follow-up date (January 31, 2007) if no events occurred. Age-adjusted survival curves were estimated from the Cox model. To generate the age-adjusted failure free survival curves, age was categorized as < 65 years or ≥65 years of age. Three statistical models were generated for the predictor variables: 1) a bivariate (crude) model for all predictors, 2) an age-adjusted model for all predictors, and 3) a multivariate model. A $p < 0.10$ in bivariate analysis was used as the criteria for inclusion of predictors in the multivariate Cox proportional hazards regression models to assess the effect of pretreatment prognostic factors on failure free survival. No significant age group (<65 vs. ≥65 years of age) interaction effect ($p > 0.05$) with the other predictors was found; thus, age-adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) were computed. Due to the limited data available, it was not possible to run an interaction model with all the predictors; however, an evaluation for the possible interaction effect between the clinical stage (I vs. II & III) with the other predictors in the model was carried out and no significant interactions were observed ($p > 0.05$); thus, multivariate HR and (95%CI) were calculated. The evaluation of the proportional hazards assumption was assessed prior to the selection of the final regression model. All statistical analyses were performed using STATA version 11 (STATA Corp., College Station, TX).

Results

Table 1 summarizes the demographic and clinical characteristics of cancer patients. Proportion of males and female cases was 54% vs. 46%, respectively. The mean age ± SD was 62.2 ± 10.4. Among the 99 with rectal adenocarcinoma,

52.4% were moderately to poorly differentiated carcinomas, and 13.1% were mucin producing tumors. Preoperative CEA level ≥ 5ng/ml was observed in 11.1%. Preoperative clinical stages of the cases were as follow: 33.3% stage I, 45.5% stage II, and 21.2% stage III. Male patients presented with a statistically significant higher rate of clinical stage II-III presentations compared to female patients (65.6% vs. 34.3%, respectively; p-value<0.01) (data not shown).

Table 1. Demographical and clinical characteristics of rectal cancer cases (n=99).

Pre-treatment factors	n (%)
Gender	
Female	46 (46.5)
Male	53 (53.5)
Age, years	
Mean (SD)	62.2 (10.4)
Median	65.0
25th-, 75th -percentiles	57, 73
Histology	n=91
Well differentiated	43 (47.2)
Moderately differentiated	44 (48.4)
Poorly differentiated	4 (4.4)
Mucin producing	
Yes	13 (13.1)
Preoperative clinical stage	
I	33 (33.3)
II	45 (45.5)
III	21 (21.2)
Preoperative CEA level, ng/ml	
≥5	11 (11.1)
<5	88 (88.9)
Lymphovascular invasion	n=69
Yes	19 (27.5)
Level in rectum†	
High (11-15cm)	18 (18.2)
Mid (6-10cm)	36 (36.3)
Low (0-5 cm)	45 (45.5)
Distance from anal verge, cm	
Mean (SD)	7.3 (3.4)
Median	7.0
Minimum-Maximum	1.0-15.0
Type of surgery	
APR	27 (27.3)
LAR	64 (64.7)
Other‡	8 (8.1)
Preoperative chemotherapy + radiotherapy	
Yes	70 (70.7)

Values are frequency "n" (percentages, "%") unless otherwise stated; SD: standard deviation; CEA: carcinoembryonic antigen; APR: abdominoperineal resection; LAR: lower anterior resection; †Measured from anal verge; ‡Other types of surgery included pelvic exanteration, subtotal colectomy

Preoperative chemotherapy and radiotherapy was used in 70.7% of the rectal cases. Of the 29 cases who did not receive preoperative chemoradiation, 26 (90%) presented with preoperative stage I, while 63 (90%) of the 70 cases who did receive preoperative chemoradiation presented with preoperative stage II or III. Thus, the use of preoperative chemoradiation was heavily weighted in favor of those who had more advanced preoperative stages. Low rectal presentation was seen in 45.5% of the patients, and the median distance from the anal verge was 9 cm.

EUS was performed primarily in the low and mid cases 25/36 (69%) and 19/45 (40%) respectively while only 3/11 (27%) of the high rectal cases had this study performed. By EUS criteria, 26 (55%) of the 47 patients who underwent this procedure were found to have localized disease (uN0) and the remaining 21 (45%) had uN1-2 disease. With the additional use of CT scans, another patient was found to have ctN1-2 disease for a total of 22/47 (47%).

In a comparison analysis of selected pretreatment factors for patients with rectal adenocarcinomas (n=99) or colon adenocarcinomas treated by the same surgeons (n=76), a higher proportion of preoperative CEA level ≥ 5 ng/ml was observed among colon patients compared to rectal cases (p<0.01) whereas a trend for a higher percentage of male patients was observed among rectal cases compared to colon cancer cases (56% vs. 44%, p=0.07) (data not shown). Both groups were similar in other selected pretreatment factors such as age, histologic grade and mucin-producing tumors.

Failure free survival analysis

Of the 99 rectal adenocarcinoma patients, 18 (18.2%) relapsed. The median follow-up time of non-relapsed patients was 36.3 months (range, 0.4 to 82.1 months). Of relapsed patients, 6 (27%) were local failures (two of whom simultaneously relapsed systemically) and the remainder were exclusively systemic. The local failure rate was 5.1%. The median failure free survival time was 31.6 months.

Figure 1 shows the age-adjusted failure free survival estimates of selected pretreatment predictors. Failure free survival was significantly different for gender (p=0.01), mucin producing tumors (p=0.02), clinical stage (p=0.02) (Figure 1; A, B and C). A marginal difference was observed in the Kaplan-Meier failure free survival estimates for CEA level (p= 0.14) (Figure 1, D).

Table 2 shows the bivariate, age-adjusted and multivariate Cox proportional hazards regression models for rectal adenocarcinoma failure free survival. In bivariate analysis, male gender (HR [95% CI]: 3.61 [1.18-10.98]), mucinous type (HR [95% CI]: 3.19 [1.11-9.13]), and clinical stages II & III (HR [95% CI]: 9.30 [1.24-69.94]) were associated with poorer failure free survival. There was a marginal trend towards a poor failure free survival in patients with CEA levels ≥ 5 ng/ml (HR [95% CI]: 3.08 [1.00-9.53]; p=0.05). The preoperative factors age, histologic grade, lymphovascular invasion, distance from the anal verge, and type of surgery performed were not associated with a poor failure free survival. In age-adjusted analysis, a significant association was maintained for male gender (HR [95CI%]: 3.32 [1.09-10.13]), mucin producing tumors (HR [95CI%]: 3.67 [1.25-10.77]), and clinical stage

(HR [95CI%]: 8.19 [1.08-62.08]). A tendency towards a poorer prognosis among patients with preoperative CEA levels ≥5 ng/ml was observed although the differences were not statistically significant [HR (95%CI): 2.46 (0.77-7.83). In age-adjusted multivariate Cox regression analysis, a tendency towards a poor prognosis was observed for male gender (HR: 2.60), mucinous type carcinoma (HR: 3.67), clinical stages II & III (HR: 4.96), and CEA levels ≥5 ng/ml (HR=2.55) was observed.

Table 2. Hazard ratios estimates and 95% confidence intervals for pretreatment factors associated with poor outcomes in rectal adenocarcinoma (N=99).

Predictors	Bivariate model HR (95% CI)	Age-adjusted model HR (95% CI)	Multivariate model† HR (95% CI)
Gender (Male)	3.61 (1.18-10.98)	3.32 (1.09-10.13)	2.60 (0.80-8.40)
Histologic grade (moderately to poorly differentiated)	2.36 (0.83-6.73)	2.02 (0.71-5.79)	-
Mucinous type	3.19 (1.11-9.13)	3.67 (1.25-10.77)	2.96 (0.97-8.98)
Clinical stage (Stages II & III)	9.30 (1.24-69.94)	8.19 (1.08-62.08)	4.96 (0.62-39.95)
Preoperative CEA ≥5 ng/ml	3.08 (1.00-9.53)	2.46 (0.77-7.83)	2.55 (0.75-8.62)
Lymphovascular invasion	1.43 (0.87-2.35)	1.38 (0.84-2.26)	-
Distance from anal verge (>5cm)	1.28 (0.73-2.25)	1.32 (0.74-2.38)	-
Type of surgery performed (APR)	0.70 (0.31-1.60)	0.73 (0.31-1.72)	-

*Multivariate model was age-adjusted, model R2: 0.13; HR: Hazard ratio; CI: Confidence interval; CEA: carcinoembryonic antigen ; APR: abdominoperineal resection

Discussion

Recent case series reveal that the majority of patients with rectal cancer can be cured (11, 60-62). The chemotherapy regimen most commonly used as part of the chemoradiation strategy is single agent 5-FU. The toxicity associated with this drug is relatively low when compared with more recent and more effective combination regimens such as FOLFOX and FOLFIRI (12-13). Consequently it is undesirable to use these more toxic regimens to treat all patients with rectal cancer. Individualization of therapy would entail the accurate selection

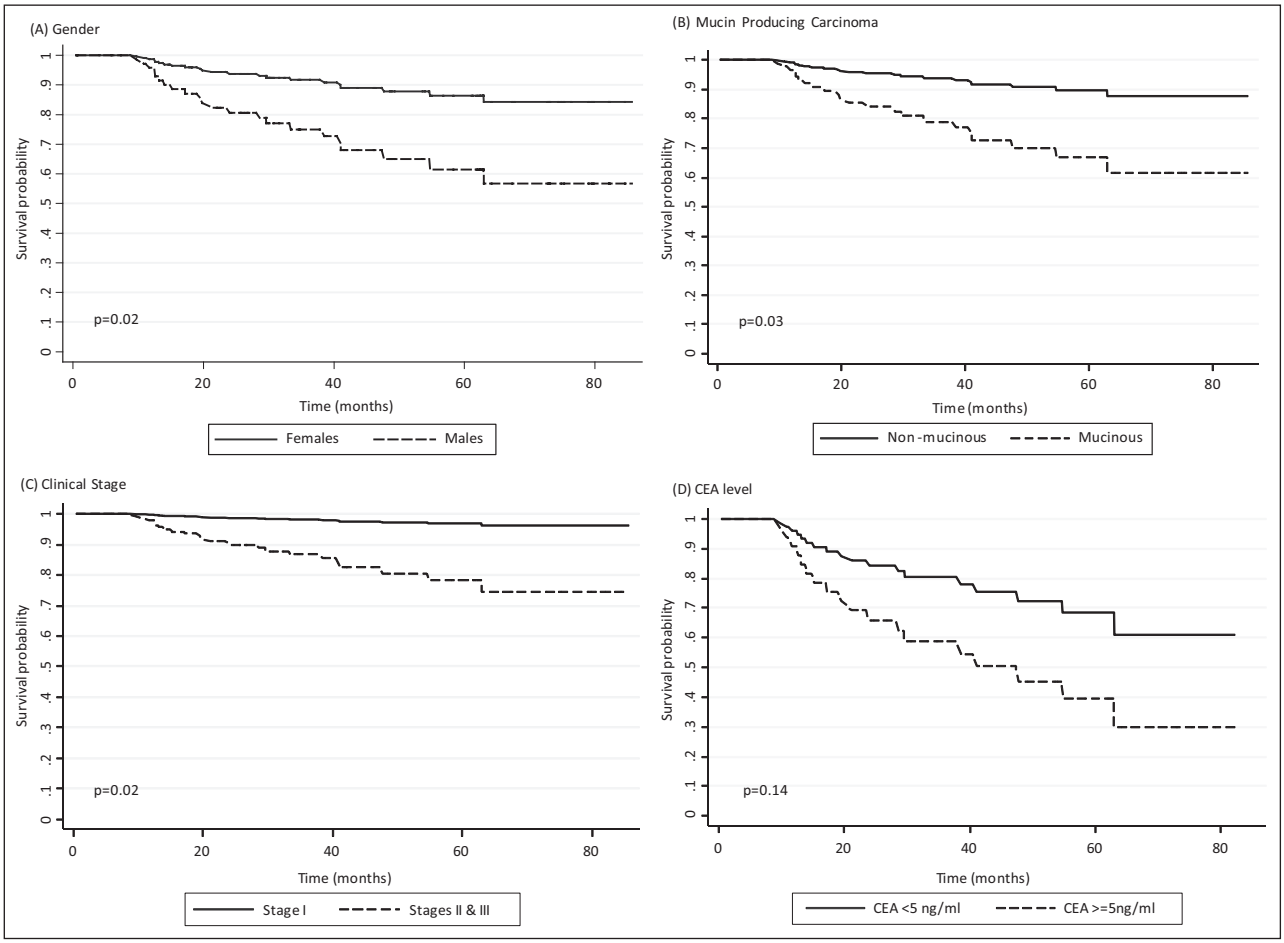

Figure 1. Age-adjusted survival curves from the Cox model for (A) gender, (B) mucinous carcinoma, (C) clinical stage, and (D) carcinoembryonic antigen (CEA) level. Statistical differences were observed for gender, mucinous type, and clinical stage (p<0.05). No differences were observed by CEA levels (p>0.05).

of those cases with poor prognostic features at diagnosis. The choice of chemotherapy regimen in rectal cancer is made prior to surgery whereas in colon cancer it is made postoperatively after the pathological stage has been determined. Thus, it is crucial to identify the pertinent pretreatment prognostic factors in rectal cancer in order to appropriately select the chemotherapy regimen. Most studies that have examined prognostic factors in rectal cancer have included postoperative factors such as the pathological response to chemoradiation. Several other studies have also recognized preoperative CEA level, gender, preoperative clinical stage, and mucinous histology as having prognostic importance. Yet, to the best of our knowledge, no studies have examined these factors using multivariable analysis strictly in the preoperative setting. Neither have any studies looked at all these prognostic factors considering rectal carcinomas separately from colon cancers. Mucinous histology has been identified as an adverse factor in some series but not in others (29, 38, 46-47, 52, 63). Our data suggest that perhaps some of the conflicting results are due to the fact that in the majority of the published literature, colon and rectal carcinomas were analyzed together without considering them as different entities thus leading to this confusion. Du et al examined the importance of mucinous histology in rectal carcinomas separately from colon (46) and their findings and conclusions are in accordance with ours in the sense that mucinous histology has an adverse impact on outcome in rectal but not in colon adenocarcinomas.

The importance of a preoperative CEA level > 5 has been shown before by several investigators and no conflicting data exist in this regard (16-17, 19, 22, 24, 30, 39, 44-45, 64-65). The explanation for this finding could be related to the biology of colorectal tumors. Human colorectal carcinomas with a preoperative CEA > 5 have a higher tumorigenic capability than those with a low CEA. This has been shown in a study using nude mice transplanted with human colorectal carcinomas derived from patients with as well as without elevated CEA preoperatively (66).

An intriguing finding from this study is the favorable outcome of females with rectal cancer. This appears to be at least in part related to the more advanced presentation seen in male patients. Preoperative stage II-III presentation was more common in males than in females. This, however, does not fully explain the inferiority in failure free survival seen in males because the multivariate Cox regression analysis still selected gender as a prognostic factor independent of preoperative clinical stage. Another possible explanation for their poor outcome is the narrower male pelvis which makes the operation more difficult. However, if that is the case, then we would expect more local relapses in males but the vast majority of failures in our series were systemic and not local, thus making this a less likely explanation for the unfavorable outcome of males. Finally, we find it intriguing that the importance of gender as a prognostic factor in rectal cancer was not observed in 126 patients with colon cancer operated by the same surgeons (data not shown).

Limitations of this study include the retrospective nature of the study design and the relatively small numbers. On the basis of our results, we recommend that further studies be conducted to assess these correlations in a larger number of patients.

In summary, our results suggest that three simple and readily available factors, CEA levels ≥5 ng/ml, male gender, and clinical stage, potentially could be used to identify patients whose predicted outcome is unfavorable. We could identify these patients preoperatively and within the setting of a clinical trial treat them with a potentially more effective experimental chemoradiation regimen. However, our conclusions are derived from a multivariate model that has not been confirmed yet in an independent population of patients with rectal cancer. Until that is done, our findings have to be considered as preliminary. In addition, even though the model is robust with a highly significant p value, it is derived from a relatively small population.

Resumen

Objetivo: En la mayoría de los países, la elección del esquema de quimioterapia a usarse para el tratamiento del cáncer rectal se hace antes de la cirugía en contraste con el cáncer de colon en donde se hace después de la operación cuando ya se ha determinado el estadío patológico de la enfermedad. Si pudiéramos identificar cuáles son los factores pronósticos pertinentes, podríamos entonces seleccionar los pacientes con cáncer rectal con características desfavorables para entonces poder investigar regímenes nuevos de quimioterapia preoperatorios potencialmente más eficaces. Este estudio presente tuvo como objetivo determinar cuáles son los factores pronósticos preoperatorios en cáncer rectal que se asocian con un resultado desfavorable. Métodos: Se realizó una revisión retrospectiva de 99 pacientes con cáncer rectal operados en el Hospital Auxilio Mutuo, San Juan, Puerto Rico y el Hospital de San Pablo, Bayamón, Puerto Rico. Se recogieron las características demográficas, los datos clínicos y el tratamiento. Resultados: El 54% de los pacientes eran varones. La media de edad ± SD fue de 62.2 ± 10.4. En un modelo de Cox ajustado por edad, el sexo masculino [HR (95% IC): 3.32 (01.09 a 10.13)], carcinoma mucinoso (HR [95% IC]: 3.67 [1.25-10.77]), y los estadios clínicos II y III ([HR 95% IC]: 8.19 [1.08-62.08]) fueron predictores de mal pronóstico. En el análisis multivariado ajustado por edad, se identificó una tendencia hacia un peor pronóstico en pacientes de sexo masculino (HR: 2,60) CEA ≥ 5ng/ml (HR: 2.55), carcinoma mucinoso (HR: 2.96), y estadios clínicos II y III (HR: 4.96), aunque los resultados no fueron estadísticamente significativos (p> 0.05). Conclusión: A pesar de que los resultados terapéuticos actuales son relativamente favorables con el uso de 5-fluorouracilo (5-FU) preoperatorio

combinado con radioterapia, los ensayos clínicos futuros deberían abordar el tema del manejo de aquellos pacientes con factores de mal pronóstico de modo que estos pacientes puedan ser tratados con esquemas de quimioterapia potencialmente más eficaces aunque más tóxicos.

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References

1. Havenga K, Enker WE, Norstein J, et al. Improved survival and local control after total mesorectal excision or D3 lymphadenectomy in the treatment of primary rectal cancer: an international analysis of 1411 patients. Eur J Surg Oncol 1999;25:368-74.
2. Nesbakken A, Nygaard K, Westerheim O, et al. Local recurrence after mesorectal excision for rectal cancer. Eur J Surg Oncol 2002;28:126-34.
3. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet 1986;1:1479-82.
4. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. Lancet 1993;341:457-60.
5. Enker WE, Thaler HT, Cranor ML, et al. Total mesorectal excision in the operative treatment of carcinoma of the rectum. J Am Coll Surg 1995;181:335-46.
6. Bolognese A, Cardi M, Muttillo IA, et al. Total mesorectal excision for surgical treatment of rectal cancer. J Surg Oncol 2000;74:21-3.
7. Martling AL, Holm T, Rutqvist LE, et al. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. Stockholm Colorectal Cancer Study Group, Basingstoke Bowel Cancer Research Project. Lancet 2000;356:93-6.
8. Marks GJ, Marks JH, Mohiuddin M, et al. Radical Sphincter preservation surgery with coloanal anastomosis following high-dose external irradiation for the very low lying rectal cancer. Recent Results Cancer Res 1998;146:161-74.
9. Chen ET, Mohiuddin M, Brodovsky H, et al. Downstaging of advanced rectal cancer following combined preoperative chemotherapy and high dose radiation. Int J Radiat Oncol Biol Phys 1994;30:169-75.
10. Janjan NA, Khoo VS, Abbruzzese J, et al. Tumor downstaging and sphincter preservation with preoperative chemoradiation in locally advanced rectal cancer: the M. D. Anderson Cancer Center experience. Int J Radiat Oncol Biol Phys 1999;44:1027-38.
11. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-40.
12. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 2000;18:2938-47.
13. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004;22:229-37.
14. Calvo FA, Serrano FJ, Diaz-Gonzalez JA, et al. Improved incidence of pT0 downstaged surgical specimens in locally advanced rectal cancer (LARC) treated with induction oxaliplatin plus 5-fluorouracil and preoperative chemoradiation. Ann Oncol 2006;17:1103-10.
15. Chau I, Brown G, Cunningham D, et al. Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging-defined poor-risk rectal cancer. J Clin Oncol 2006;24:668-74.
16. Oh JH, MacLean LD. Prognostic use of preoperative and immediate postoperative carcinoembryonic antigen determinations in colonic cancer. Can J Surg 1977;20:64-7.
17. Wolmark N, Fisher B, Wieand HS, et al. The prognostic significance of preoperative carcinoembryonic antigen levels in colorectal cancer. Results from NSABP (National Surgical Adjuvant Breast and Bowel Project) clinical trials. Ann Surg 1984;199:375-82.
18. Steinberg SM, Barwick KW, Stablein DM. Importance of tumor pathology and morphology in patients with surgically resected colon cancer. Findings from the Gastrointestinal Tumor Study Group. Cancer 1986;58:1340-5.
19. Scott NA, Wieand HS, Moertel CG, et al. Colorectal cancer. Dukes' stage, tumor site, preoperative plasma CEA level, and patient prognosis related to tumor DNA ploidy pattern. Arch Surg 1987;122:1375-9.
20. Minsky BD, Mies C, Recht A, et al. Resectable adenocarcinoma of the rectosigmoid and rectum. II. The influence of blood vessel invasion. Cancer 1988;61:1417-24.
21. Wiggers T, Arends JW, Schutte B, et al. A multivariate analysis of pathologic prognostic indicators in large bowel cancer. Cancer 1988;61:386-95.
22. Wiggers T, Arends JW, Volovics A. Regression analysis of prognostic factors in colorectal cancer after curative resections. Dis Colon Rectum 1988;31:33-41.
23. Deans GT, Patterson CC, Parks TG, et al. Colorectal carcinoma: importance of clinical and pathological factors in survival. Ann R Coll Surg Engl 1994;76:59-64.
24. Slentz K, Senagore A, Hibbert J, et al. Can preoperative and postoperative CEA predict survival after colon cancer resection? Am Surg 1994;60:528-31; discussion 31-2.
25. Hermanek P, Wiebelt H, Staimmer D, et al. Prognostic factors of rectum carcinoma--experience of the German Multicentre Study SGCRC. German Study Group Colo-Rectal Carcinoma. Tumori 1995;81:60-4.
26. Martijn H, de Neve W, Lybeert ML, et al. Adjuvant postoperative radiotherapy for adenocarcinoma of the rectum and rectosigmoid. A retrospective analysis of locoregional control, survival, and prognostic factors on 178 patients. Am J Clin Oncol 1995;18:277-81.
27. Cusack JC, Giacco GG, Cleary K, et al. Survival factors in 186 patients younger than 40 years old with colorectal adenocarcinoma. J Am Coll Surg 1996;183:105-12.
28. Wolters U, Stutzer H, Isenberg J. Gender related survival in colorectal cancer. Anticancer Res 1996;16:1281-9.
29. Wu CS, Tung SY, Chen PC, et al. Clinicopathological study of colorectal mucinous carcinoma in Taiwan: a multivariate analysis. J Gastroenterol Hepatol 1996;11:77-81.
30. Harrison LE, Guillem JG, Paty P, et al. Preoperative carcinoembryonic antigen predicts outcomes in node-negative colon cancer patients: a multivariate analysis of 572 patients. J Am Coll Surg 1997;185:55-9.
31. Reiter W, Stieber P, Reuter C, et al. Prognostic value of preoperative serum levels of CEA, CA 19-9 and CA 72-4 in gastric carcinoma. Anticancer Res 1997;17:2903-6.
32. Blumberg D, Paty PB, Picon AI, et al. Stage I rectal cancer: identification of high-risk patients. J Am Coll Surg 1998;186:574-9; discussion 9-80.
33. Cyvoct C, Quantin C, Broet P, et al. [Prognostic factors of recurrence and/or death in colorectal cancer: multistate modeling]. Rev Epidemiol Sante Publique 1999;47:619-25.
34. Janjan NA, Abbruzzese J, Pazdur R, et al. Prognostic implications of response to preoperative infusional chemoradiation in locally advanced rectal cancer. Radiother Oncol 1999;51:153-60.
35. Park YJ, Youk EG, Choi HS, et al. Experience of 1446 rectal cancer patients in Korea and analysis of prognostic factors. Int J Colorectal Dis 1999;14:101-6.
36. Compton C, Fenoglio-Preiser CM, Pettigrew N, et al. American Joint Committee on Cancer Prognostic Factors Consensus Conference: Colorectal Working Group. Cancer 2000;88:1739-57.
37. Compton CC, Fielding LP, Burgart LJ, et al. Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. Arch Pathol Lab Med 2000;124:979-94.

38. Consorti F, Lorenzotti A, Midiri G, et al. Prognostic significance of mucinous carcinoma of colon and rectum: a prospective case-control study. J Surg Oncol 2000;73:70-4.
39. Wang WS, Lin JK, Chiou TJ, et al. Preoperative carcinoembryonic antigen level as an independent prognostic factor in colorectal cancer: Taiwan experience. Jpn J Clin Oncol 2000;30:12-6.
40. Chmielarz A, Kryj M, Wloch J, et al. Prognostic factors for the time of occurrence and dynamics of distant metastases and local recurrences after radical treatment in patients with rectal cancer. Med Sci Monit 2001;7:1263-9.
41. Mitry E, Benhamiche AM, Jouve JL, et al. Colorectal adenocarcinoma in patients under 45 years of age: comparison with older patients in a well-defined French population. Dis Colon Rectum 2001;44:380-7.
42. Di Betta E, D'Hoore A, Filez L, et al. Sphincter saving rectum resection is the standard procedure for low rectal cancer. Int J Colorectal Dis 2003;18:463-9.
43. Garcia-Aguilar J, Hernandez de Anda E, Sirivongs P, et al. A pathologic complete response to preoperative chemoradiation is associated with lower local recurrence and improved survival in rectal cancer patients treated by mesorectal excision. Dis Colon Rectum 2003;46:298-304.
44. Bannura G, Cumsille MA, Contreras J, et al. [Carcinoembryonic antigen (CEA) as an independent prognostic factor in colorectal carcinoma]. Rev Med Chil 2004;132:691-700.
45. De Vita F, Orditura M, Lieto E, et al. Elevated perioperative serum vascular endothelial growth factor levels in patients with colon carcinoma. Cancer 2004;100:270-8.
46. Du W, Mah JT, Lee J, et al. Incidence and survival of mucinous adenocarcinoma of the colorectum: a population-based study from an Asian country. Dis Colon Rectum 2004;47:78-85.
47. Papadopoulos VN, Michalopoulos A, Netta S, et al. Prognostic significance of mucinous component in colorectal carcinoma. Tech Coloproctol 2004;8(Suppl 1):s123-5
48. Pucciarelli S, Toppan P, Friso ML, et al. Complete pathologic response following preoperative chemoradiation therapy for middle to lower rectal cancer is not a prognostic factor for a better outcome. Dis Colon Rectum 2004;47:1798-807.
49. Bamias A, Basdanis G, Xanthakis I, et al. Prognostic factors in patients with colorectal cancer receiving adjuvant chemotherapy or chemoradiotherapy: a pooled analysis of two randomized studies. Int J Gastrointest Cancer 2005;36:29-38.
50. Chapet O, Romestaing P, Mornex F, et al. Preoperative radiotherapy for rectal adenocarcinoma: Which are strong prognostic factors? Int J Radiat Oncol Biol Phys 2005;61:1371-7.
51. Chen CC, Yang SH, Lin JK, et al. Is it reasonable to add preoperative serum level of CEA and CA19-9 to staging for colorectal cancer? J Surg Res 2005;124:169-74.
52. Negri FV, Wotherspoon A, Cunningham D, et al. Mucinous histology predicts for reduced fluorouracil responsiveness and survival in advanced colorectal cancer. Ann Oncol 2005;16:1305-10.
53. Diaz-Gonzalez JA, Calvo FA, Cortes J, et al. Prognostic factors for disease-free survival in patients with T3-4 or N+ rectal cancer treated with preoperative chemoradiation therapy, surgery, and intraoperative irradiation. Int J Radiat Oncol Biol Phys 2006;64:1122-8.
54. Park YA, Lee KY, Kim NK, et al. Prognostic effect of perioperative change of serum carcinoembryonic antigen level: a useful tool for detection of systemic recurrence in rectal cancer. Ann Surg Oncol 2006;13:645-50.
55. Renzulli P, Lowy A, Maibach R, et al. The influence of the surgeon's and the hospital's caseload on survival and local recurrence after colorectal cancer surgery. Surgery 2006;139:296-304.
56. Stipa F, Chessin DB, Shia J, et al. A pathologic complete response of rectal cancer to preoperative combined-modality therapy results in improved oncological outcome compared with those who achieve no downstaging on the basis of preoperative endorectal ultrasonography. Ann Surg Oncol 2006;13:1047-53.
57. Collette L, Bosset JF, den Dulk M, et al. Patients with curative resection of cT3-4 rectal cancer after preoperative radiotherapy or radiochemotherapy: does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the European Organisation for Research and Treatment of Cancer Radiation Oncology Group. J Clin Oncol 2007;25:4379-86.
58. Wiig JN, Larsen SG, Dueland S, et al. Preoperative irradiation and surgery for local recurrence of rectal and rectosigmoid cancer. Prognostic factors with regard to survival and further local recurrence. Colorectal Dis 2008;10:48-57.
59. Robey-Cafferty SS, el-Naggar AK, Grignon DJ, et al. Histologic parameters and DNA ploidy as predictors of survival in stage B adenocarcinoma of colon and rectum. Mod Pathol 1990;3:261-6.
60. Gerard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol 2006;24:4620-5.
61. Guillem JG, Chessin DB, Cohen AM, et al. Long-term oncologic outcome following preoperative combined modality therapy and total mesorectal excision of locally advanced rectal cancer. Ann Surg 2005;241:829-36; discussion 36-8.
62. Gerard A, Buyse M, Nordlinger B, et al. Preoperative radiotherapy as adjuvant treatment in rectal cancer. Final results of a randomized study of the European Organization for Research and Treatment of Cancer (EORTC). Ann Surg 1988;208:606-14.
63. Kang H, O'Connell JB, Maggard MA, et al. A 10-year outcomes evaluation of mucinous and signet-ring cell carcinoma of the colon and rectum. Dis Colon Rectum 2005;48:1161-8.
64. Boonpipattanapong T, Chewatanakornkul S. Preoperative carcinoembryonic antigen and albumin in predicting survival in patients with colon and rectal carcinomas. J Clin Gastroenterol 2006;40:592-5.
65. Lo Gerfo P, Herter FP. Carcinoembryonic antigen and prognosis in patients with colon cancer. Ann Surg 1975;181:81-4.
66. Mentges B. Colon carcinoma. Preoperative CEA, tumor differentiation and prognosis. Dtsch Med Wochenschr 1987;112:1245-9.